24. (amended) [The method of claim 16] A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor, wherein the compound is an antibody or antibody fragment immunoreactive with the receptor.

Remarks

Claim 24 has been rewritten in independent form in view of the statement that claims 24-26 are objected to as dependent upon a rejected claim, but otherwise allowable.

Rejections under 35 U.S.C. 112

Claims 16 and 17 were rejected under 35 U.S.C. 112 as not supported by the specification. This rejection is respectfully traversed if applied to the amended claims.

Claim 17 has been amended to refer to nucleotide sequences which encode proteins or peptides inhibiting binding. There is a great deal of support in the application for how to make and use such nucleotide sequences, although the examiner is correct that the intent here is not to claim the use of oligonucleotides as the actual inhibitors *per se* which bind to the receptor protein. Support is found in the section entitled "*Preparation of Receptor Protein Fragments*".

The examiner has rejected the claims that are drawn to other than antibodies and antibody fragments on the basis that there is no description of other proteins that block binding. This is not accurate. First, those skilled in the art would have been fully enabled to make all or part of the receptor protein based on the sequence which is

disclosed and methods and reagents available from commercial or scientific sources. The section referred to above, *Preparation of Receptor Protein Fragments*, fully supports the use of such peptides to block binding. See, for example,

> "Compounds which are effective for blocking binding of the receptor can also consist of fragments of the receptor proteins, expressed recombinantly and cleaved by enzymatic digest or expressed from a sequence encoding a peptide of less than the full length receptor protein. These will typically be soluble proteins, i.e., not including the transmembrane and cytoplasmic regions, although smaller portions determined in the assays described above **to inhibit or compete** for binding to the receptor proteins can also be utilized. It is a routine matter to make appropriate receptor protein fragments, test for binding, and then utilize. The preferred fragments are of human origin, in order to minimize potential immunological response. The peptides can be as short as five to eight amino acids in length and are easily prepared by standard techniques. They can also be modified to increase *in vivo* half-life, by chemical modification of the amino acids or by attachment to a carrier molecule or inert substrate. Based on studies with other peptide fragments blocking receptor binding, the IC_{50}, the dose of peptide required to inhibit binding by 50%, ranges from about 1 μM to greater than 10 mM, depending on the peptide size and folding. These ranges are well within the effective concentrations for the *in vivo* administration of peptides, based on

comparison with the RGD-containing peptides, described, for example, in U.S. Patent No. 4,792,525 to Ruoslaghti, et al., used *in vivo* to alter cell attachment and phagocytosis. "

The examiner has provided no factual or literature support for the statement that such assays would require undue experimentation. He has acknowledged that applicants have provided sufficient information to obtain antibodies and antibody fragments. Using the many libraries of peptides that are available, it would be no more than routine experimentation to run these libraries through the same screening assays - either they inhibit the receptor binding, or they do not. Nothing more is required.

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing* In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.
>
> *Id.* at § 2164.05 (emphasis added).

In this case, the examiner is relying on conclusory statements without putting forth specific reasons describing why the claims are not enabled by the specification. The

patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure **and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.** Otherwise, there would be no need for the Appellant to go to the trouble and expense of supporting his presumptively accurate disclosure.
>
> *Id.* at 224.

The MPEP instructs examiners to make specific findings of *facts* to rebut Appellants' presumption and "specifically identify what information is missing and why one of skill in the art could not supply the information without undue experimentation." MPEP at § 2164.05. The examiner should provide references to support a *prima facie* case of lack of enablement. *Id.*

The Examiner has failed to meet the legal burden in this case.

Allowance of claims 16, 17 and 24-30, is therefore earnestly solicited.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION (37 CFR 1.8a)

I hereby certify that this , along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the Assistant Commissioner for Patents, Washington, D.C. 20231, on the date shown below.

Date: June 26, 2002 Peggy Bailey

Peggy Bailey

APPENDIX: Marked Up Copy of the Claims as Amended

16. (amended) A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor.

17. (amended) The method of claim 16 wherein the compound is selected from the group consisting of antibodies and fragments of antibodies to the receptor, nucleic acid sequences encoding proteins or peptides inhibiting expression of the receptor, and synthetic or natural compounds other than proteins, peptides or nucleic acid sequences which inhibit binding.

24. (amended) [The method of claim 16] A method for enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor comprising administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor by binding to the endothelial cell protein C/activated protein C receptor, wherein the compound is an antibody or antibody fragment immunoreactive with the receptor.

25. The method of claim 24 wherein the antibody is humanized.

26. The method of claim 16 wherein the compound is labeled.

27. The method of claim 16 wherein the compound is an oligonucleotide.

28. The method of claim 16 wherein the compound is a receptor fragment.

29. The method of claim 16 wherein the compound is combined with a pharmaceutically acceptable carrier.

30. The method of claim 16 wherein the compound is administered in an amount effective to enhance an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor.